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Shy-Drager syndrome: the transitional variant

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Abstract. The clinicopathological features of a patient with the transitional variant of the Shy-Drager syndrome is described. The only previously reported case of the transitional variant was reexamined and pathological similarities to the present case are reviewed. Both patients exhibited features of Parkinson's disease with Lewy bodies in the substantia nigra and locus ceruleus. Striato-nigral degeneration and olivo-ponto-cerebellar atrophy were evident in both cases. They can thus be considered as transitional forms of the Shy-Drager syndrome with feature of both Parkinson's disease and multiple system atrophy.

Key words: Shy-Drager syndrome - Parkinson's disease - multiple system atrophy - transitional variant

Introduction

Shy-Drager syndrome was first described in 1960 [Shy and Drager] and is characterized by a progressive failure of autonomic function associated with other neurological disturbances [Graham and Oppenheimer 1969, Spokes et al. 1979, Bannister and Oppenheimer 1982]. Shy and Drager [1960] reviewed the literature and reported on the neuroanatomical findings and reiterated the common clinical features so that their names have continued to remain associated with the syndrome. The striking clinical features are orthostatic hypotension accompanied by anhidrosis, urinary incontinence, sexual impotency and a disturbance of voluntary movements. Bannister and Oppenheimer [1972] reported four patients with postural hypotension of 3-6 years duration, all of whom demonstrated on initial presentation either urinary frequency, urinary incontinence or sexual impotence. Additional clinical signs common to all patients at an advanced stage of the disease included nystagmus, dysarthria, extrapyramidal rigidity and facial immobility.

The characteristic neuropathological finding is a loss of up to 90 % of the sympathetic neurons of the intermediolateral nucleus of the spinal cord [Vanderhaeghen et al. 1970, Bannister and Oppenheimer 1972 and 1982, Spokes et al. 1979]. Further neuropathological changes in Shy-Drager syndrome have led to the separation of two distinct groups; 1) those with changes characteristic of Parkinson's disease (PD), and 2) those with multiple system atrophy (MSA). The MSA group has been further subdivided into two types: a) the olivo-ponto-cerebellar type and b) the striatonigral type [Bannister and Oppenheimer 1982]. The same authors recently reviewed 42 cases with detailed neuropathologic examinations and found 10 cases of the PD group and 32 cases of the MSA group. The PD group acquired the disease at an older age, showing a mean age at death of 72 years, whereas the MSA group affected younger patients, with a mean age of 58 years at the time of death [Bannister and Oppenheimer 1982]. The one exception to the above categorization is a single case reported by Thapedi et al. [1971] which was transitional showing features of both PD and MSA. We describe the clinical features and the neuropathological findings in a second patient with the transitional variant. The pathologic findings in the previously reported case was reexamined and the features common to the two cases are emphasized.

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Case Reports

Case I

Clinical Course

A 68-year-old Caucasian male first presented in 1978, after a fall in an elevator. He was hospitalized at the Health Sciences Centre, Winnipeg, and the diagnosis of Shy-Drager syndrome was entertained. He had been in good health without any evidence of urinary incontinence or sexual impotence. He was provided with elastic stockings and given indomethacin and florinef. He improved markedly over a three-week period and was

taken off medications. In October 1979, he experienced frequent episodes of collapse on assuming on upright position. The previous medications were again prescribed but were not effective in controlling the symptoms. In January 1980, he began to notice urinary incontinence. Postural hypotension became progressively more debilitating with increased frequency of collapse, although he tended to recover spontaneously within one to two minutes.

He was readmitted in February 1980 with increased urinary frequency, urinary incontinence, throbbing headaches and a dry mouth unassociated with dysphagia. There were no accompanying visual disturbances, paralysis, or parethesias. No tremor or features of extra-pyramidal rigidity were identified.

Digital skin temperature testings were within normal limits. Tilt table testing revealed a sharp fall in blood pressure from 190/70 in the supine to 70/40 mmHg in the standing position. The postural change caused only a minimal increase in pulse rate. Recovery of blood pressure on return to the supine position was rapid.

Blood samples for renin assays were drawn in a supine and sitting position. The increase in renin concentration from 0.1 to 0.5 pmol/l/s was considered adequate. The patient was discharged and readmitted in January 1982. He had experienced syncopes at least twice a day for the last four weeks and was unable to move for at least ten minutes after collapsing to the floor. He was on a multiple drug regimen that included oxybutynin chloride and indomethacin. He now demonstrated lateral and rotary nystagmus, and abnormalities of convergence. He described labored breathing and a chest x-ray revealed chronic interstitial pneumonia. He demonstrated marked dysarthria and dysphagia and his speech was difficult to comprehend. Cogwheel rigidity was present. A Valsalva maneuver indicated a fall of 30 mmHg in phase two and reflex vasoconstriction failed to occur in phase four. There was no change in heart rate noted during the test. Neurological examination also revealed intention tremor most marked in the upper limbs. The patient continued to deteriorate and died of bilateral bronchopneumonia 13 days after admission.

Neuropathology

The brain weighed 1,360 g. There was no evidence of cortical atrophy. The meninges were unremarkable. The spinal cord showed no gross abnormalities. Coronal sections of the cerebrum revealed atrophy and brown discoloration of the putamen. On sectioning no abnormalities were seen in the cerebellum. The brainstem showed marked pallor of the substantia nigra.

Microscopic examination showed severe neuronal loss and gliosis of the putamen (Figure 1). The globus pallidus showed moderate neuronal loss and gliosis. The substantia nigra showed severe loss of pigmented neurons

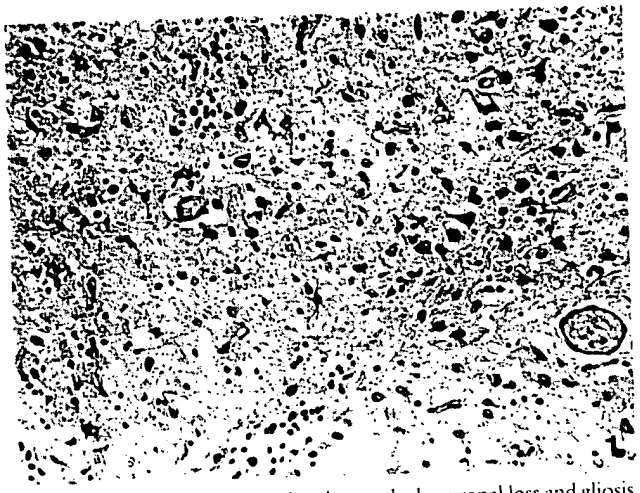

Fig. 1 Section from putamen showing marked neuronal loss and gliosis. Case I (hematoxylin-eosin, × 184).

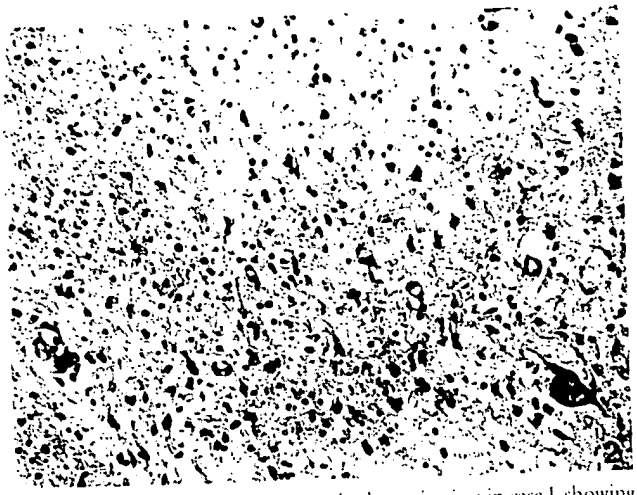

Fig. 2 Histological view of the lateral substantia nigra in case I, showing severe neuronal loss and gliosis (hematoxylin-eosin, × 184).

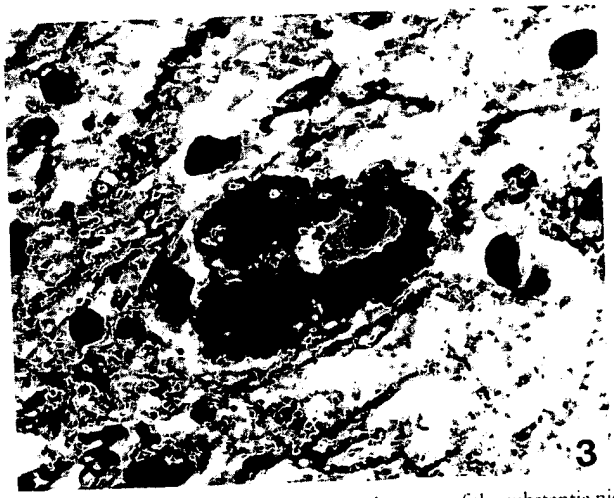

Fig. 3 Mature Lewy body in a pigmented neuron of the substantia nigra in case I (hematoxylin-eosin, × 980).

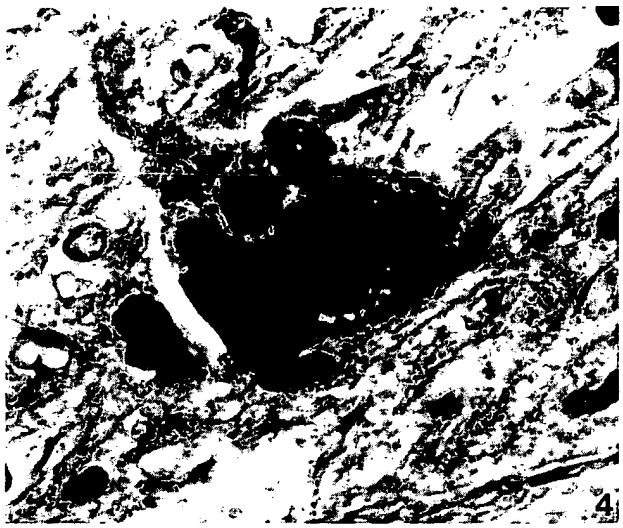

Fig. 4 Pigmented neuron of the locus ceruleus in case I showing two mature Lewy-bodies (hematoxylin-eosin, × 1,280).

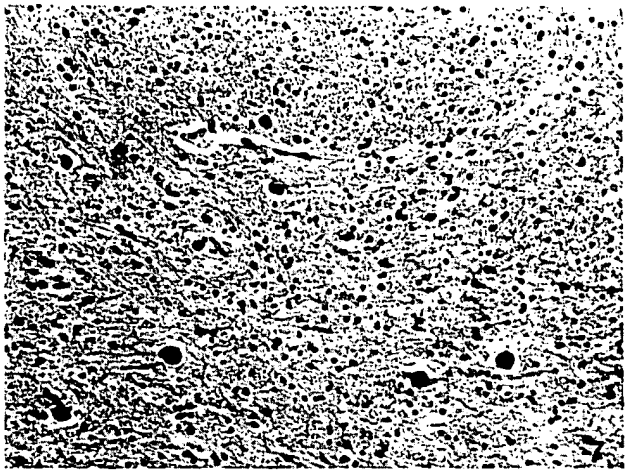

Fig. 7 The pontine nuclei in case I showing a moderate neuronal loss and gliosis (hematoxylin-eosin, × 184).

Fig. 5 Detail of the nucleus basalis of Meynert in case I demonstrating an early Lewy body (hematoxylin-eosin, × 980).

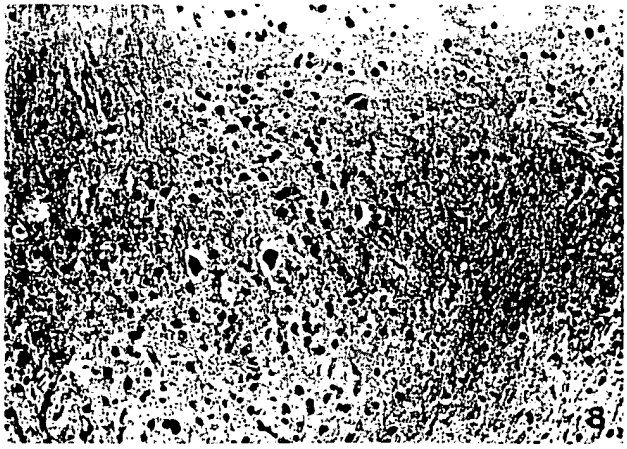

Fig. 8 The inferior olivary nucleus showed mild neuronal loss and gliosis in case I (hematoxylin-eosin, × 184).

Fig. 6 Low power view of cerebellum illustrating Purkinje cell loss and moderate Bergman gliosis. Case I (hematoxylin-eosin, × 74).

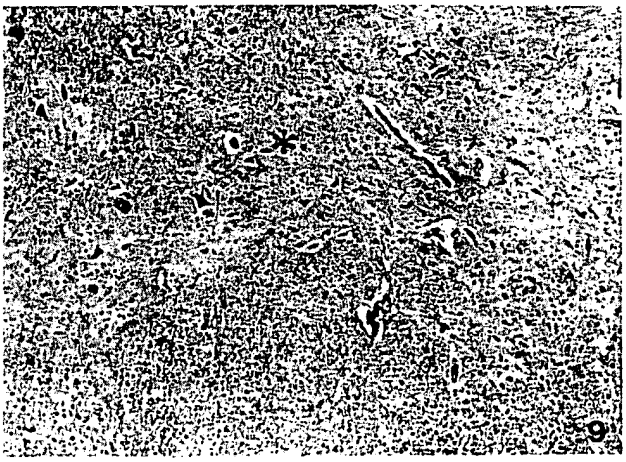

Fig. 9 Neuronal loss and moderate gliosis are demonstrated in the intermediolateral nucleus (asterix) at T_9–T_{10} in case I (hematoxylin-eosin, × 120).

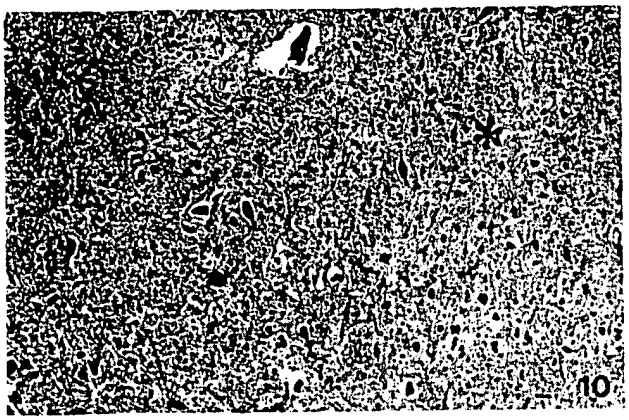

Fig. 10 The Edinger-Westphal nucleus (asterix) in case I showing neuronal loss and gliosis (hematoxylin-eosin, × 120).

and gliosis particularly in the lateral two thirds of the nucleus (Figure 2). Numerous cytoplasmic inclusions consistent with early Lewy bodies were seen. Only after multiple step sections through the nucleus could classical Lewy bodies be demonstrated (Figure 3). The locus ceruleus showed marked neuronal loss and the occasional Lewy body (Figure 4). The nucleus basalis of Meynert showed mild neuronal loss and early Lewy bodies (Figure 5). The cerebellum demonstrated a moderate loss of Purkinje cells, Bergman gliosis, and occasional torpedos in the internal granular cell layer (Figure 6). The pontine nuclei and the inferior olivary nuclei showed a mild to moderate neuronal loss (Figures 7 and 8). The dorsal nucleus of vagus showed mild neuronal loss but no Lewy bodies or early Lewy bodies.

Sections of the spinal cord at T_1–T_2 and T_9–T_{10} showed neuronal loss and moderate gliosis of the intermediolateral nucleus (Figure 9). Cell counts compared with an age-matched control section revealed a 60% loss. The neuronal population in the anterior horns was unremarkable. The Edinger-Westphal nucleus showed marked nerve cell loss, gliosis and early Lewy bodies (Figures 10 and 11). Cell counts revealed a 50% loss.

Case II

The clinical and pathological features were previously described by Thapedi at al. [1971]. Sections from the pons, cerebellum, locus ceruleus, dorsal nucleus of vagus, substantia nigra, Edinger-Westphal nucleus and the nucleus basalis of Meynert were reexamined. Typical and early Lewy bodies were seen in the locus ceruleus and substantia nigra. Early Lewy bodies were seen in the Edinger-Westphal nucleus, and in the nucleus basalis of Meynert. The dorsal motor nucleus of the vagus showed severe neuronal loss, gliosis and early Lewy bodies. As

System involvements	Anatomical sites of involvement	Case I	Case II
Autonomic involvement /neuronal loss/	Intermediolateral nucleus	++	++
	Edinger-Westphal nucleus	++	++
	Dorsal nucleus of vagus	+	++
Parkinson's disease /Lewy bodies/ (Lewy-like bodies)	Substantia nigra	+ (++)	++ (+)
	Locus ceruleus	++ (+)	+ (+)
	Dorsal nucleus of vagus	− (−)	− (+)
	Basal nucleus of Meynert	− (++)	− (+)
Multiple system atrophy /neuronal loss/	Putaman Globus pallidus Substantia nigra	+++ ++ ++	+ − +
	Cerebellum Pons Inferior olivary nucleus	++ ++ +	+++ ++ ++
	Anterior horn cells	−	+

Table I Degree of neuropathological change in the two present cases of the transitional variant of Shy-Drager syndrome.

+ mild, ++ moderate, +++ severe, − normal

Fig. 11 A neuron of the Edinger-Westphal nucleus showing an early Lewy body and with laterally displaced nucleus. Case I (hematoxylin-eosin, × 980).

previously documented, there was a marked loss of Purkinje cells in the cerebellum. The superior olivary nucleus and the pontine nuclei showed marked neuronal loss. The spinal cord revealed a marked nerve cell loss in the intermediolateral nucleus in the thoracic region. Neuronal cell count revealed a 70% loss. The Edinger-Westphal nucleus showed a 45% loss of neurons and moderate gliosis.

The neuropathological findings in the two cases are summarized in Table 1.

Discussion

Postural hypotension was described by Bradbury and Eggleston in 1925. Shy and Drager [1960] later described a variety of neurological disturbances in addition to the progressive autonomic dysfunction, the constellation of which is known as Shy-Drager syndrome. It is a relatively rare degenerative disorder with a relentless course and of unknown etiology. Based mainly on neuropathological findings the syndrome can be divided into two groups; one which shows the features of Parkinson's disease and a second more varied group with multiple system involvement, usually olivo-ponto-cerebellar degeneration and/or striato nigral degeneration.

Our case I is the second case of the so-called transitional form of Shy-Drager syndrome with neuropathological stigmata of both Parkinson's disease, striato-nigral degeneration and an early stage of ponto-cerebellar degeneration. The previously described case of the transitional variant showed Parkinson's disease, olivo-ponto-cerebellar degeneration and changes consistent with mild striato-nigral degeneration.

Both cases demonstrated in the substantia nigra and the locus ceruleus Lewy bodies characteristic of Parkinson's disease. In addition, the pigmented brain stem nuclei and the basal nucleus of Meynert, as well as the Edinger-Westphal nucleus contained lightly eosinophilic cytoplasmic inclusions, with obscure central cores but without the characteristic halos of Lewy bodies. These inclusions are most amply described as immature Lewy bodies [Ikeda et al. 1978]. Case I showed, in addition, marked neuronal loss and gliosis of the putamen and to a lesser extent in the lateral globus pallidus and in the two lateral thirds of the substantia nigra. These findings are characteristic of striato-nigral degeneration, and may to some extent have obscured the presence of characteristic Lewy bodies in the substantia nigra, since several sections had to be examined for their indentification. The neuronal loss and gliosis of the putamen in case II was mild. This case on the other hand demonstrated severe Purkinje cell loss as well as neuronal loss of the pontine nuclei and the inferior olivary nuclei, consistent with olivo-ponto-cerebellar degeneration. Case I exhibited a moderate loss of both Purkinje cells and neurons of the pontine nuclei as well as mild neuronal loss in the inferior olivary nuclei, representing an early stage of olivo-ponto-cerebellar degeneration.

Unique to the present two cases were the neuronal loss and gliosis in the Edinger-Westphal nucleus which have not previously been reported in Shy-Drager syndrome [Bannister and Oppenheimer 1972].

The first case gave a history of orthostatic hypotension of less than six months duration at first presentation. Although tentatively diagnosed as having Shy-Drager syndrome, there were no overt signs of autonomic dysfunction for two years. He then developed in short succession, urinary incontinence, urinary frequency and a dry mouth. In contrast, Bannister and Oppenheimer [1972] noted the latter signs at initial presentation in their cases which was also true for case II. Both patients later developed nystagmus, dysarthria and extrapyramidal rigidity. These latter clinical findings are consistent with previous cases of Shy-Drager syndrome [Bannister and Oppenheimer 1972, Rajput and Rozdilsky 1976, Spokes et al. 1979].

The clinical findings in the two present patients with the transitional variant are thus similar to the previously described groups of patients with Shy-Drager syndrome. The clinical findings were compatible with the affected regions of the brain. Urinary frequency, dry mouth, dysarthria and dysphagia are consistently seen in patients with striato-nigral involvement [Bannister and Oppenheimer 1972]. The involvement of the Edinger-Westphal nucleus was probably responsible for the convergence abnormalities noted on eye examination in case I. The cere-

bellar findings noted on clinical examination were most likely related to the changes seen in the cerebellum, the pons and the inferior olivary nuclei.

Our older patient I, was 70 years old when he died which is in keeping with the older age of patients with Shy-Drager syndrome of the PD group, whereas patient II was younger, 58 years old at the time of death, more in keeping with the age distribution in the MSA group [Bannister and Oppenheimer 1982].

In summary, the present two cases demonstrated neuropathological changes characteristic of Shy-Drager syndrome of both the Parkinson's disease and multiple system atrophy groups and are therefore compatible with the rare goup of Shy-Drager syndrome that Bannister and Oppenheimer [1972] have referred to as transitional.

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